

Towards personalized cardiovascular prevention

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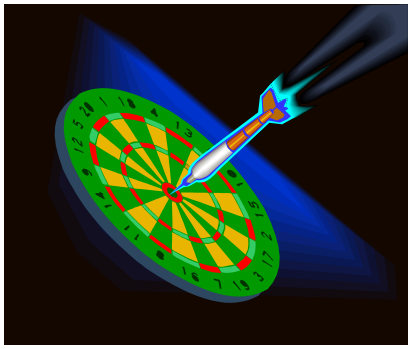
Vision for the Transformation of Medicine in the 21st Century = "P4 Medicine"

Predictive **Personalized** **Preemptive**



= PARTICIPATORY

Leading to Patient Empowerment !!

Comprehensive, genomics-based health care is going to become the norm with individualized preventive medicine and early detection of illnesses….

Personalized Medicine: Definition

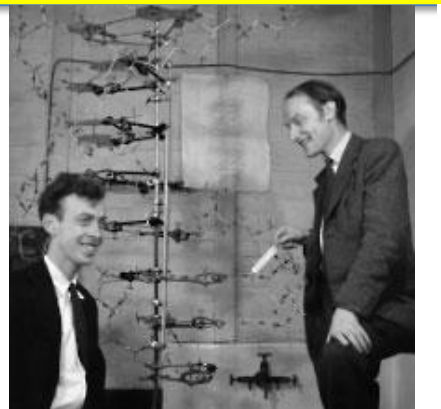
"Personalized medicine is the use of diagnostic and screening methods to better manage the individual patient's disease or predisposition toward a disease….

"Personalized medicine will enable risk assessment, diagnosis, prevention, and therapy specifically tailored to the unique characteristics of the individual, thus enhancing the quality of life and public health."

Risk Factors, Biomarkers & Genetic Markers

- Risk Factors as predictive factors
- Risk Factors as causative factors
- Markers of pathobiological events
- Markers of target organ response/damage

- Genetic / genomic markers of disease susceptibility
- Genetic / genomic markers of therapeutic response



No. 4356 April 25, 1953 NATURE 737

MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

Pharmacogenetics:

Study of the effect of variation in a single gene

Pharmacogenomics:

Study of the effect of variation in multiple genes

What can we understand from studying variations (SNPs) ?

- **Understand the risk of a child being affected by inherited disorders**
  - carrier status in the case of unaffected parents
- **Identify SNPs associated with disease development**
  - diabetes, heart disease....addiction, Alzheimer's etc.
- **Identify patients patients that will benefit from drugs**
- **Explain differential response to drugs**
  - adjust doses of drugs
- **Aid in therapeutic development**

Clinical Application of Genetic Susceptibility Information

- **Improve disease prevention**
  - Secondary prevention in those with disease
  - Primary prevention in at-risk relatives

- **Improve disease management**
  - Earlier diagnosis
  - Better prognosis

➔ **Targeted treatments**

- **Pharmacogenomics**

Coronary Artery Disease is a Complex Genetic Disease

- Multiple risk factors
- Estimated that traditional risk factors fail to explain up to 50% of CAD morbidity and mortality

- Novel risk factors are being described
- Interaction of risk factors
- **Most traditional and novel risk factors have a genetic influence**

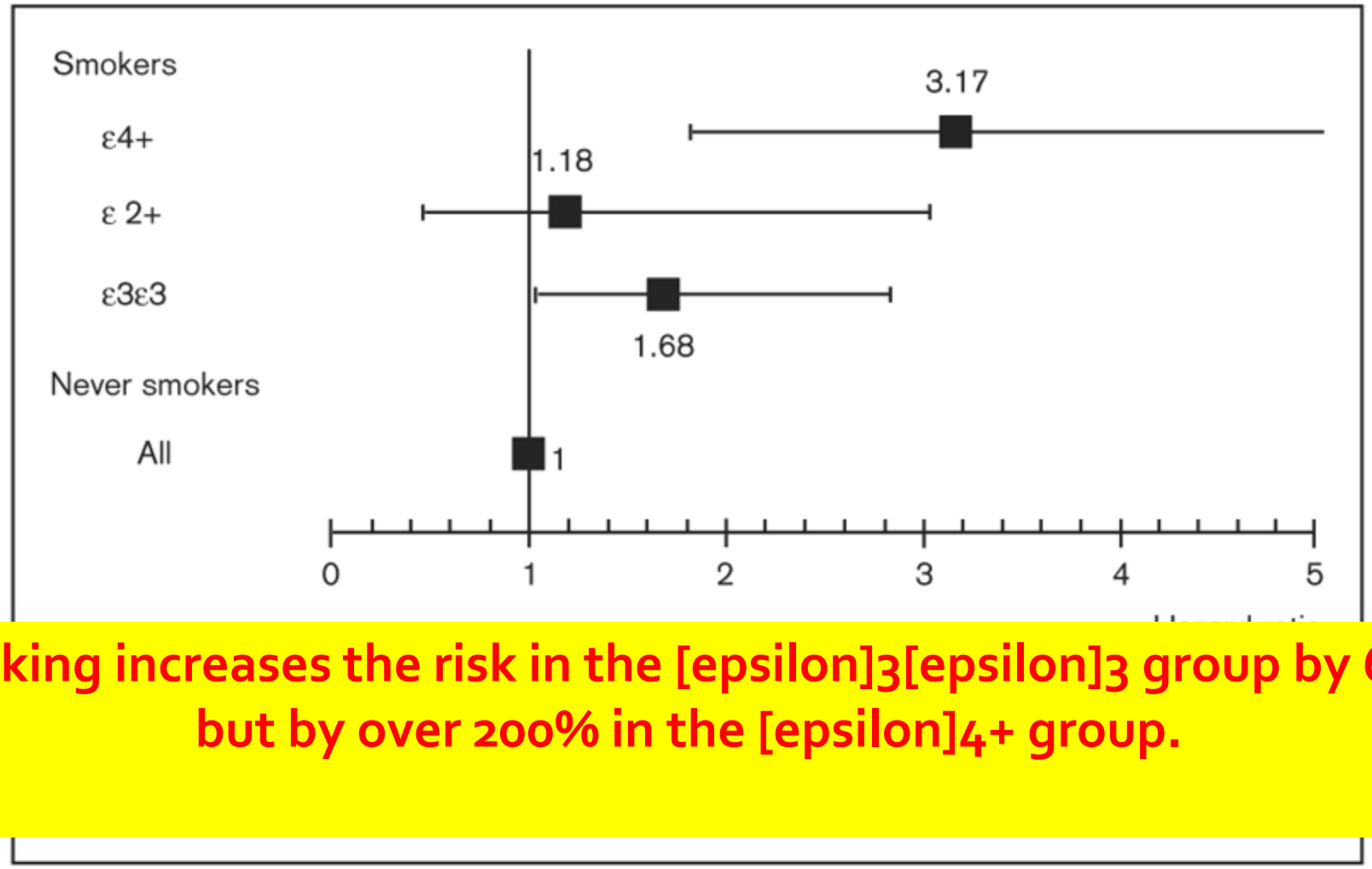
Candidate Genes for Lipid Traits from Genomic Studies

LDL	HDL	Triglycerides
APOB	ABCA1	APOA cluster
APOE cluster	CETP	ANGPTL3
LDLR	LIPC	MLXIPL
HMGCR	LIPG	GCKR
PCSK9	LPL	TRIB1
CSPG3	GALNT2	
SORT1	MVK	

From: (1) Willer et al., Nat Genet 2008: 40,161-169; (2) Kathiresan et al., Nat Genet 2008: 40,189-197;

(3) Kooner et al., Nat Genet 2008: 40,149-151; (4) Sandhu et al., Lancet 2008: 371,483-491

APOE: Smoking Interaction And Risk Of Coronary Heart Disease



Smoking increases the risk in the [epsilon]3[epsilon]3 group by 68%, but by over 200% in the [epsilon]4+ group.

The hazard ratios and 95% confidence intervals taken from the Northwick Park Heart Study, a prospective study of the risk of coronary heart disease (CHD), which has followed more than 3000 middle-aged men for over 6 years. For non-smokers all genotype groups have been pooled and the hazard ratio set at 1. In this group there were 32 CHD events and 727 event-free men. In smokers, divided on the basis of the APOE genotype, in the [epsilon]3[epsilon]3 group there were five events and 367 event-free men, in the [epsilon]4+ group there were 21 events and 163 event-free men, and for the [epsilon]2+ group there were five events and 95 event-free men.

Talmud: Curr Opin Lipidol, Volume 13(2).April 2002.149-154

Apo E Genotype Effects on Plasma Lipids

- **Apo E3 has "normal" lipid metabolism - no genotype impact**

- **Apo E2 versus Apo E4 - opposing effects on plasma lipids**
  - **Apo E2 associated with slow conversion of IDL to LDL**
    - ✓ **Decreases plasma cholesterol and increases triglycerides**
  - **Apo E4 limits HDL-binding - inhibits normal cholesterol clearance process (reverse cholesterol transport or RCT)**
    - ✓ **Increases total cholesterol, LDL, and TG and decreases HDL**

Mamotte C, et al. Am J Physiol 1999;276:E553-E557

Therapeutic Implications of Apo E

- **Interactions between Apo E gene polymorphism, abnormal lipid profiles, and diet and drug therapy have been documented**

- **Therapy targeting the lipid abnormalities resulting from the phenotypic expression of certain Apo E genotypes in response to environmental "stress" factors can mediate their impact on CVD**

Dallongeville J, et al. J Lipid Res 1992;33(4):447-54; Schaefer EJ, et al. Arterioscler Thromb 1994;14(7):1105-13; Sing CF, Davignon J. Am J Hum Genet 1985;37(2):268-85; Stengard JH, et al. Circulation 1995;91(2):265-9; Wang XL, et al. Arterioscler Thromb Vasc Biol 1995;15(8):1030-4.; Wilson PW, et al. JAMA 1994;272(21):1666-71.

Apo E Genotype and CVD Risk

	Apo E2 Response		Apo E3 Response		Apo E4 Response	
Genotype	2/2	2/3	3/3	3/4	3/4	4/4
Population Frequency	1%	10%	62%	2%	20%	5%
CVD Risk	Intermediate		Normal		Highest Risk (↑ 42%)	

Ann Intern Med 2004: 141(2): 137-47

Apo E Genotype Response
Treatment Summary

Apo E Genotype	Treatment	Surrogate Markers	Response
Apo E2	♦ Statin	♦ ↓ LDL	♦ Beneficial
	♦ Moderate Alcohol	♦ ↓ LDL / ↑ HDL	♦ Beneficial
	♦ Low Fat Diet	♦ ↑ Small Dense LDL / limited ↓ LDL	♦ Not Recommended
Apo E4	♦ Statin	♦ Limited ↓ LDL	♦ Limited
	♦ Moderate Alcohol	♦ ↑ LDL / ↓ HDL	♦ Not Recommended
	♦ Low Fat Diet	♦ ↓ LDL / ↓ TG / ↓ small dense LDL	♦ Beneficial

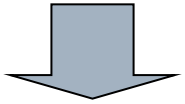
↑ Increases ↓ decreases

Therapeutic Implications of Apo E

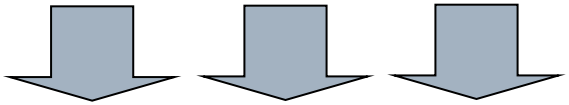
- **When managed with treatment algorithms based on the routine CVD analytes supported by consensus guidelines (without Apo E genotype), a significant percentage of patients will be:**
  - **sub-optimally treated**
  - **managed in a limited way with a "one diet, standard drug therapy regimen fits all" approach**

Apo E Genotype and CVD Management

Heterogeneity of gene-environment interaction



Heterogeneity of therapeutic response to "accepted" treatments



Establish Apo E genotyping as an important adjunct to an aggressive, targeted, and effective cardiovascular disease management program

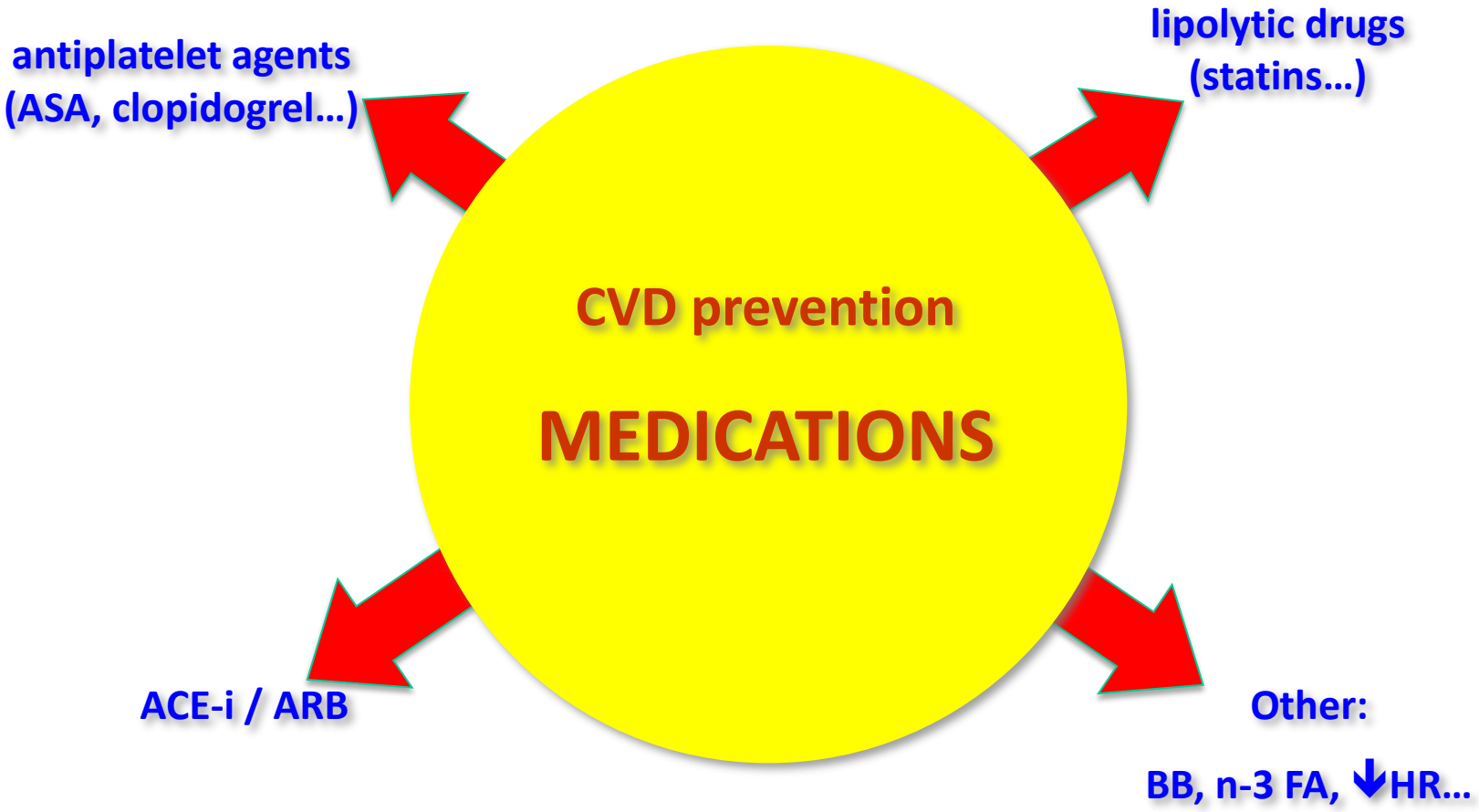
…..allowing personalization of:

- **Pharmaceutical Recommendation**
- **Diet Recommendation**
- **Alcohol Recommendation**

SNP Panels for Risk Prediction – Pitfalls

- Several companies are marketing SNP panels to the general public, charging hundreds to thousands of € / $
- The premise for these panels is that they will let patients know if they are at higher risk for particular diseases
- **None of these panels have yet been shown to add value to traditional risk factor algorithms**, and they should not be recommended to patients at this time
- The panels do not include rare mutations that cause disease

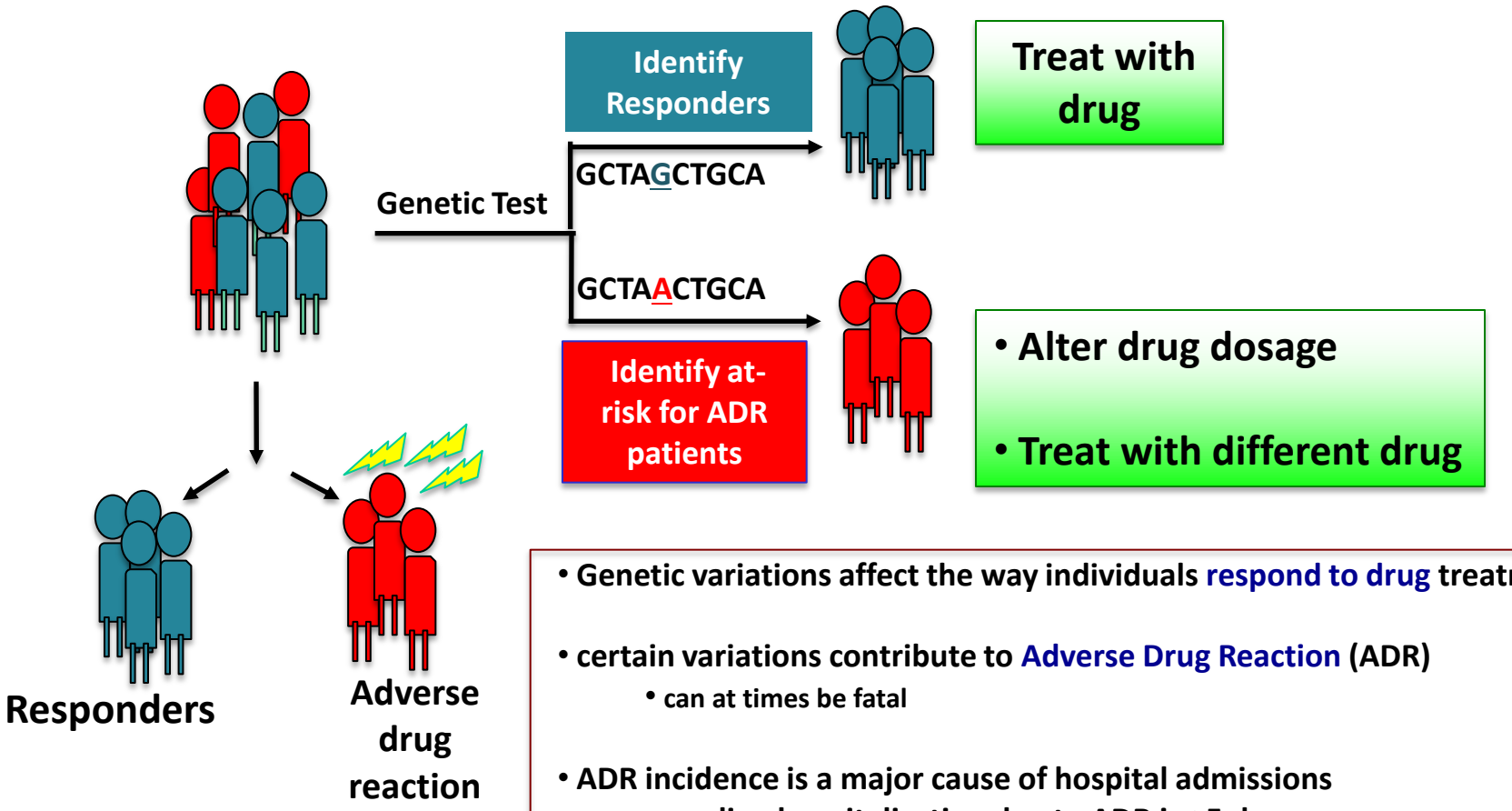
Strategies in CVD prevention: 1. lifestyle change & 2. medical (drug) intervention…..



RISK ASSESMENT

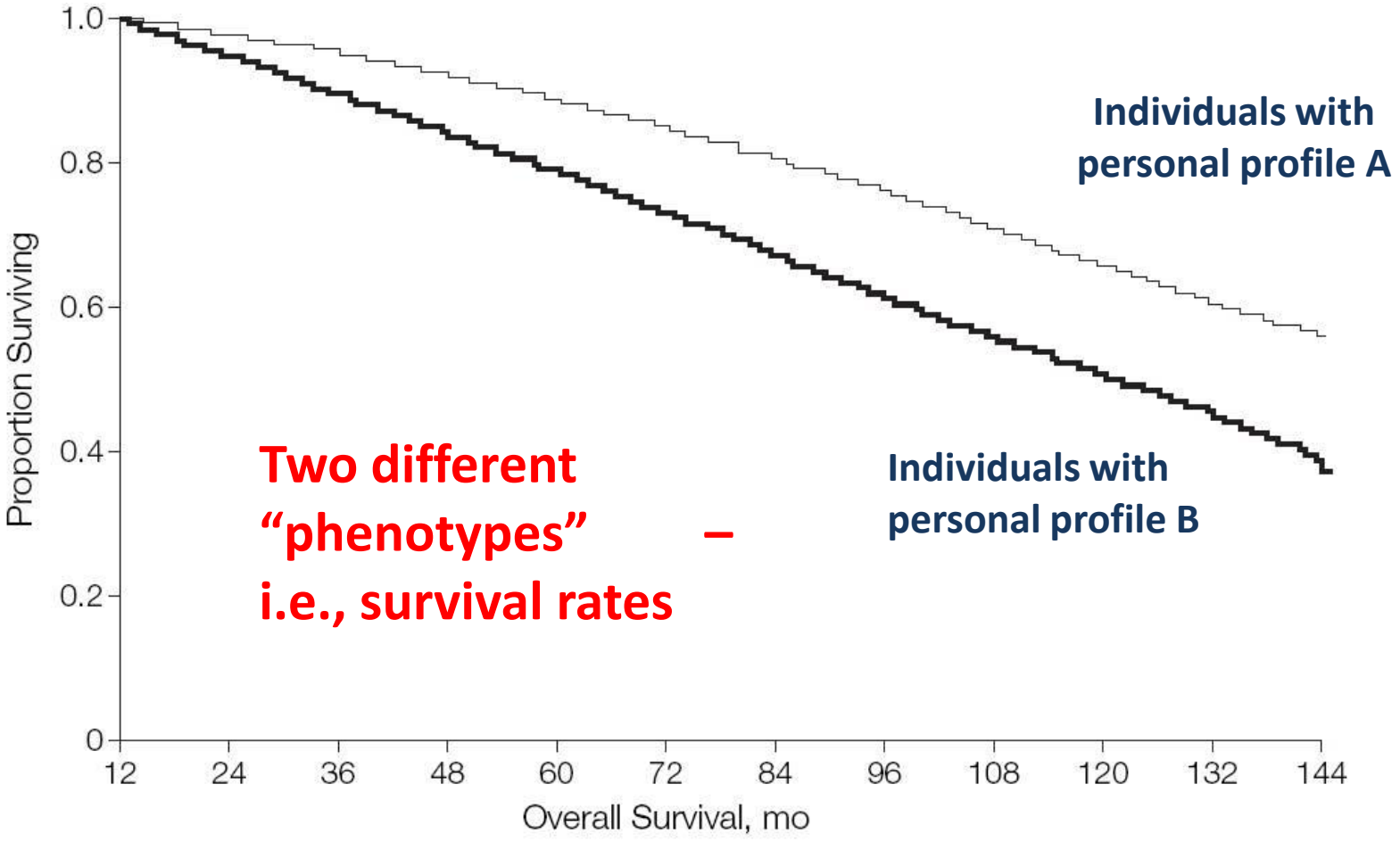
PHARMACOGENETICS → OPTIMAL THERAPY FOR INDIVIDUAL PATIENTS

Drug Response Tests



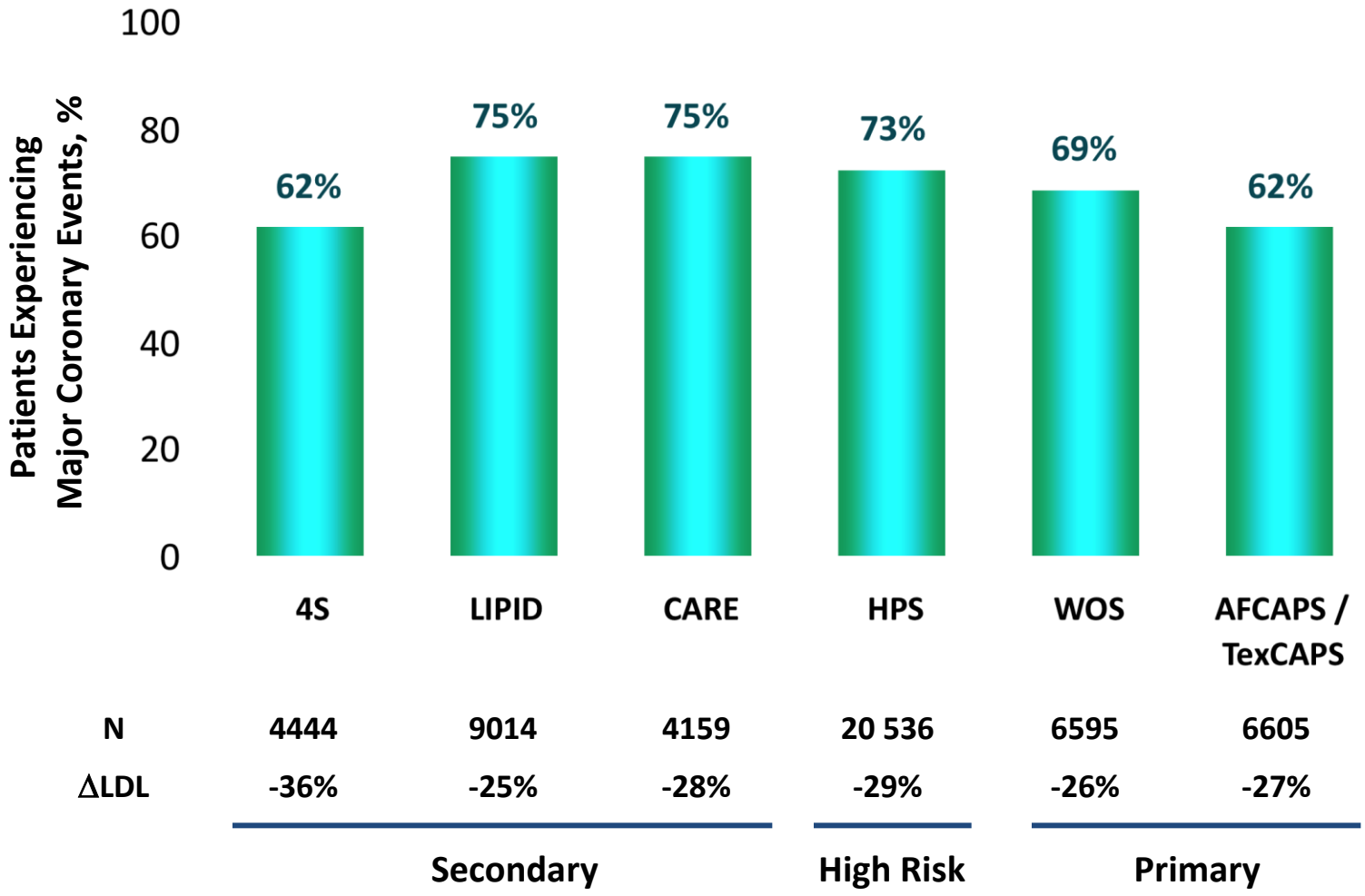
- Genetic variations affect the way individuals respond to drug treatment
- certain variations contribute to Adverse Drug Reaction (ADR)
  - can at times be fatal
- ADR incidence is a major cause of hospital admissions
  - median hospitalization due to ADR is ~5 days
  - cost INR 6197/- (USD 150) per patient.
- Testing for the variations that are linked to adverse drug reaction prior to treatment will helping doctors adjust the dose of a drug or opt for an alternate treatment.

The Challenge



Two different "phenotypes" – i.e., survival rates

Residual Cardiovascular Risk in Major Statin Trials



Libby PJ, et al. J Am Coll Cardiol, 2005:46:1225-1228.

EDITORIAL

Pharmacogenomics — Ready for Prime Time

Susan B. Shurin, M.D., and Elizabeth G. Nabel, M.D.

REVIEW ARTICLE

DRUG THERAPY

Alastair J.J. Wood, M.D., *Editor*

Pharmacogenomics — Drug Disposition, Drug Targets, and Side Effects

William E. Evans, Pharm.D., and Howard L. McLeod, Pharm.D.

Pharmacogene and Cholester

Daniel I. Chasman, PhD
David Posada, PhD

642 **Therapy and clinical trials**

Pharmacogenomics of statin response

Lara M. Mangravite and Ronald M. Krauss

Purpose of review

Although statin therapy has been shown to reduce

Introduction

Statins are prescribed for primary and secondary
cular disease (CVD) and act prim-
n in plasma LDL-cholesterol – a
VD [1–3]. The LDL-cholesterol
statin treatment is variable, with
achieve recommended reductions

Pharmacogenomics of statin safety

The genetic polymorphism of key enzymes involved in statin metabolism may be relevant to the safety and tolerability of this class of drugs [65].

Cytochrome P450 activities vary from patient to patient, and these differences may increase sensitivity to drug interactions involving competition in patients with low CYP3A4 activity [66,
of the CYP2D6 enzyme is ch
interindividual variability, and
been provided on the associ
polymorphism and the effic

The risk/benefit assessment for a drug or class of drugs (e.g. statins) has a greater relevance than assessment of safety *per se*. Indeed, safety is a relative, rather than an absolute, term: it is only when the risk clearly outweighs the benefit that clinical use can no longer be justified. At present, statins still constitute the class of hypolipidemic drugs exhibiting the most favorable risk/benefit ratio. An awareness, among patients and physicians, of both the

Statin pharmacogenomics: what have we learned, and what remains unanswered?

Kouji Kajinami[a], Mizuho Okabayashi[a], Ryoko Sato[a], Eliana Polisecki[b] and Ernst J. Schaefer[b]

KIF6 Trp719Arg and CHD

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Genetics and Coronary Artery Disease

Association of the Trp719Arg Polymorphism in Kinesin-Like Protein 6 With Myocardial Infarction and Coronary Heart Disease in 2 Prospective Trials

The CARE and WOSCOPS Trials

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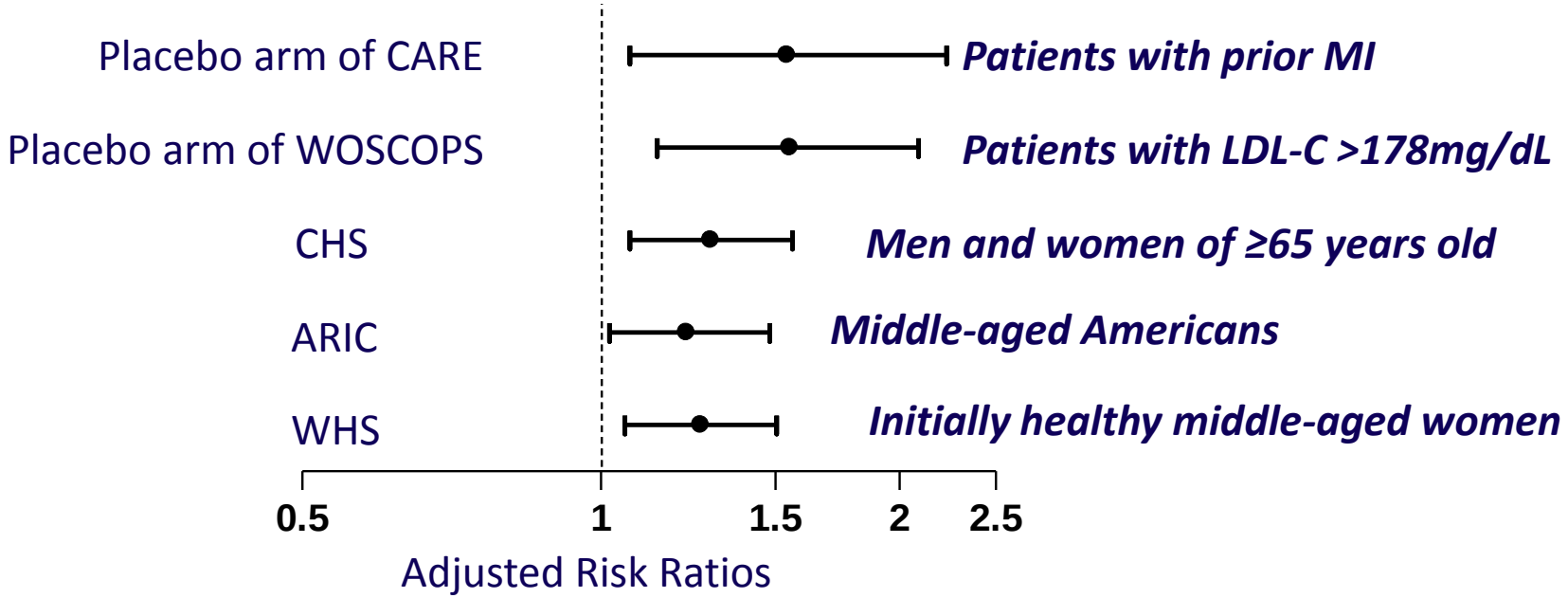
Alameda, California; Princeton, New Jersey; Boston, Massachusetts; and Glasgow, United Kingdom

- **Up to 50% increased risk of CHD in carriers of a common KIF6 variant**
  - **KIF6 719Arg is the risk variant**
  - **~60% of Caucasians carry one or two risk variant of the gene**
  - **KIF6 encodes a kinesin, a molecular motor protein**

- **Statin therapy can provide substantial and significant benefit in carriers**

Previous Genetic Studies of KIF6 719Arg

Risk of CHD in 5 Prospective Studies (>49,000 participants)



- **Carriers of the *KIF6* 719Arg variant (60% of Caucasians) are at greater risk (approx. 50%) of coronary events compared with noncarriers**

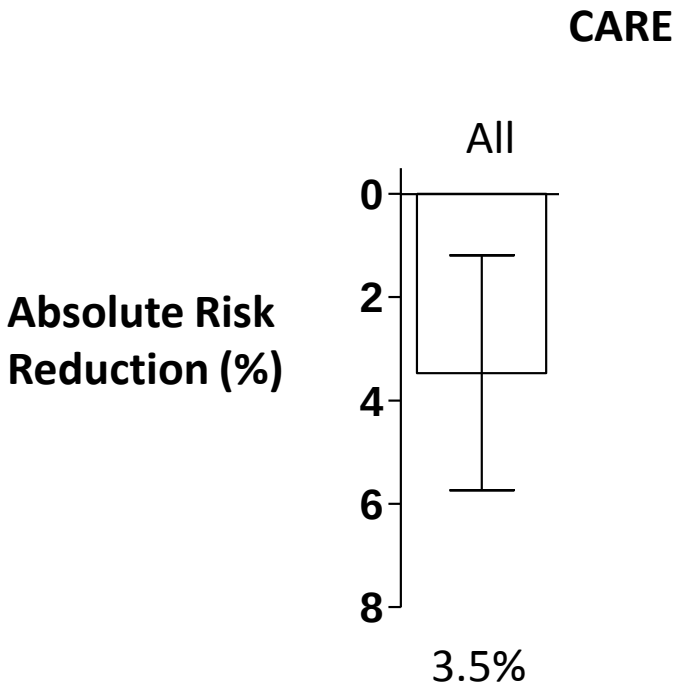
WHS: Shiffman *et al. J Am Coll Cardiol* 2008; **51**:444

ARIC: Bare *et al. Genet Med.* 2007; **10**:682

CHS: Shiffman *et al. Arterioscler Thromb Vasc Biol.* 2008; **1**:173

CHD Event Reduction by Pravastatin

According to KIF6 719Arg Carrier Status



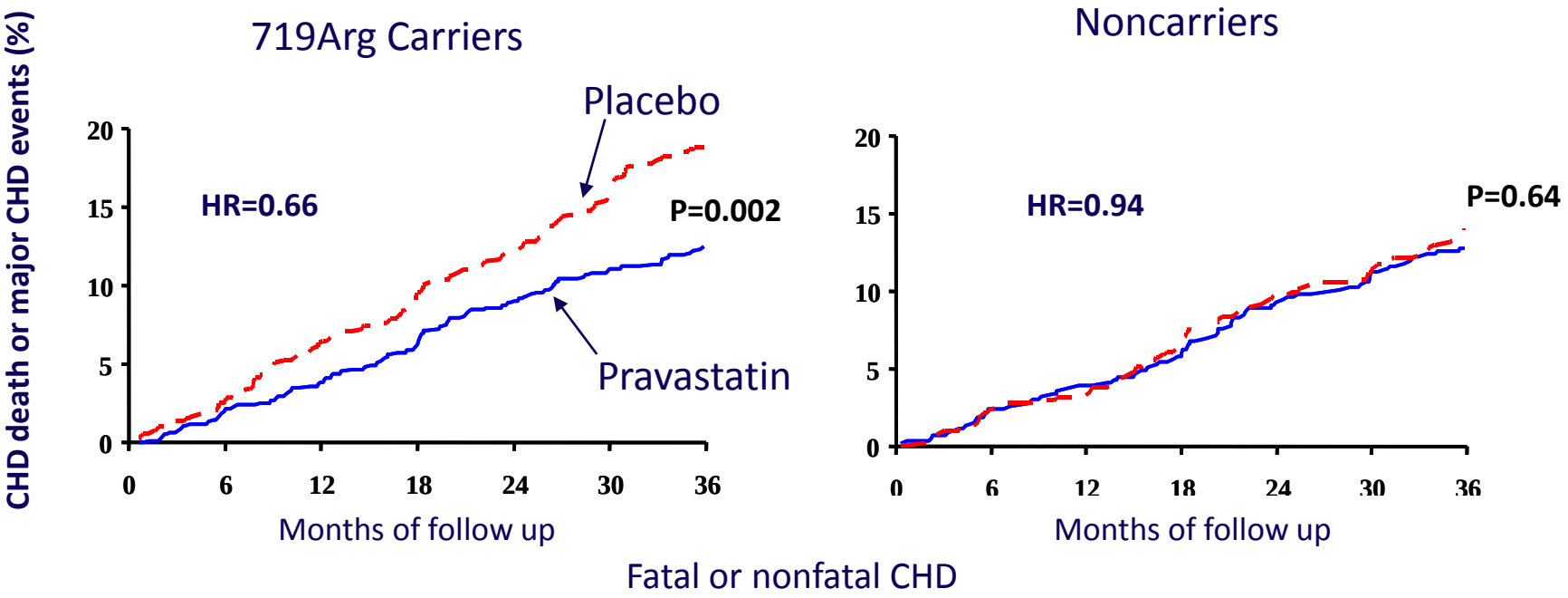
Number Needed to Treat

NNT for KIF6 in CARE and WOSCOPS

- **For prevention of coronary events with pravastatin in CARE**:
  - NNT *KIF6* carriers: 20
  - NNT noncarriers: 72

- **In WOSCOPS, the projected NNT was:**
  - 18 for *KIF6* carriers
  - >100 for noncarriers

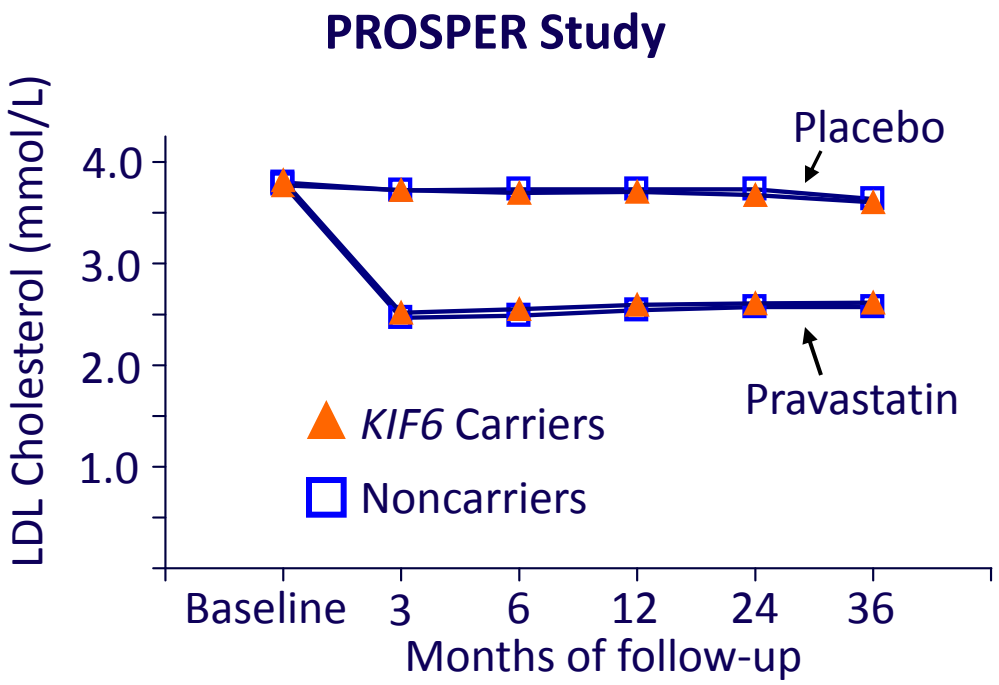
Coronary Events According to *KIF6* 719Arg Carrier Status in PROSPER Patients with Prior Vascular Disease



- **Among patients with prior vascular disease, carriers of *KIF6* 719Arg risk allele received substantial and significant reduction of coronary events, whereas noncarriers did not**
  - 34% relative risk reduction in carriers
- Among patients without prior vascular disease, no significant event reduction

LDL-C Lowering by Pravastatin Therapy

In the Elderly with Prior Vascular Disease

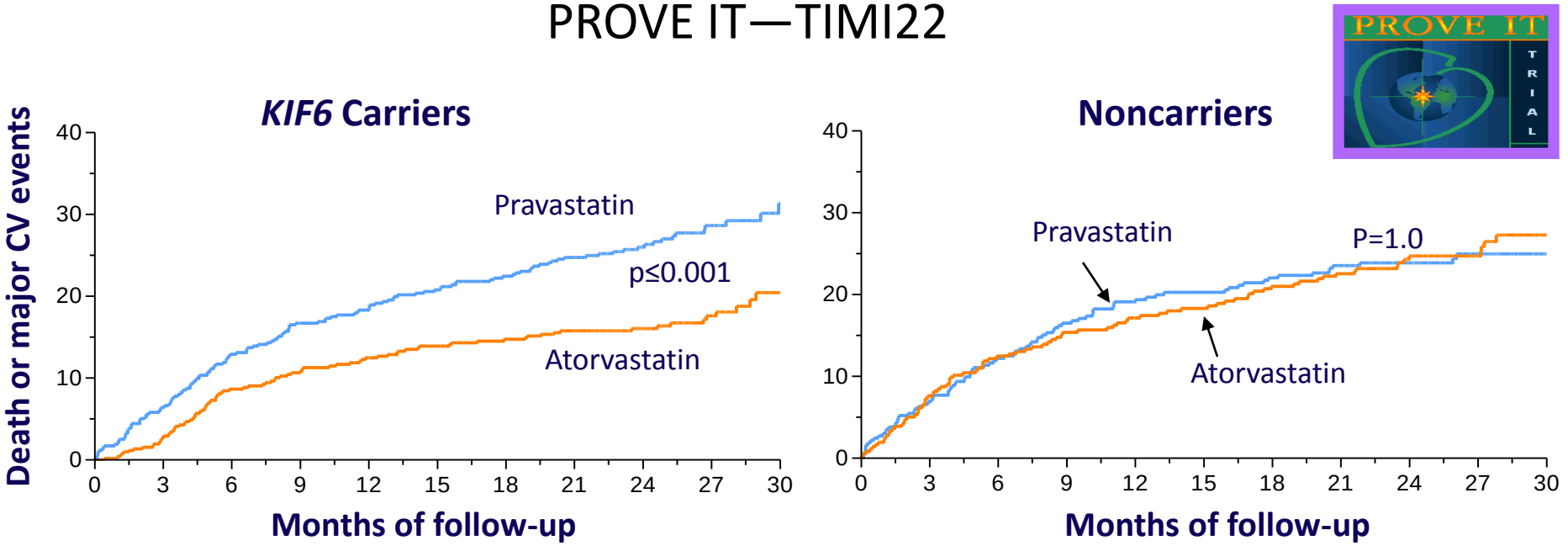


- In PROSPER, substantial and significant difference in reduction of events between carriers and noncarriers was observed despite similar reduction of LDL-C levels
- A similar observation was made in PROVE IT–TIMI 22
- An indication of the **pleiotropic effect of statins among 719Arg carriers**

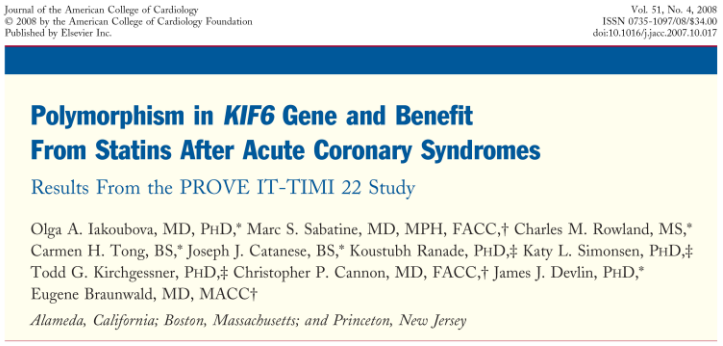
Statin Intensity and CHD Event Reduction

According to KIF6 719Arg Carrier Status

PROVE IT—TIMI22



- *KIF6* carriers received greater benefit from 80mg atorvastatin, compared with 40mg pravastatin, than did noncarriers
- NNT for atorvastatin vs pravastatin:
  - 10 for *KIF6* carriers
  - 125 for noncarriers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Polymorphism in *KIF6* Gene and Benefit From Statins After Acute Coronary Syndromes

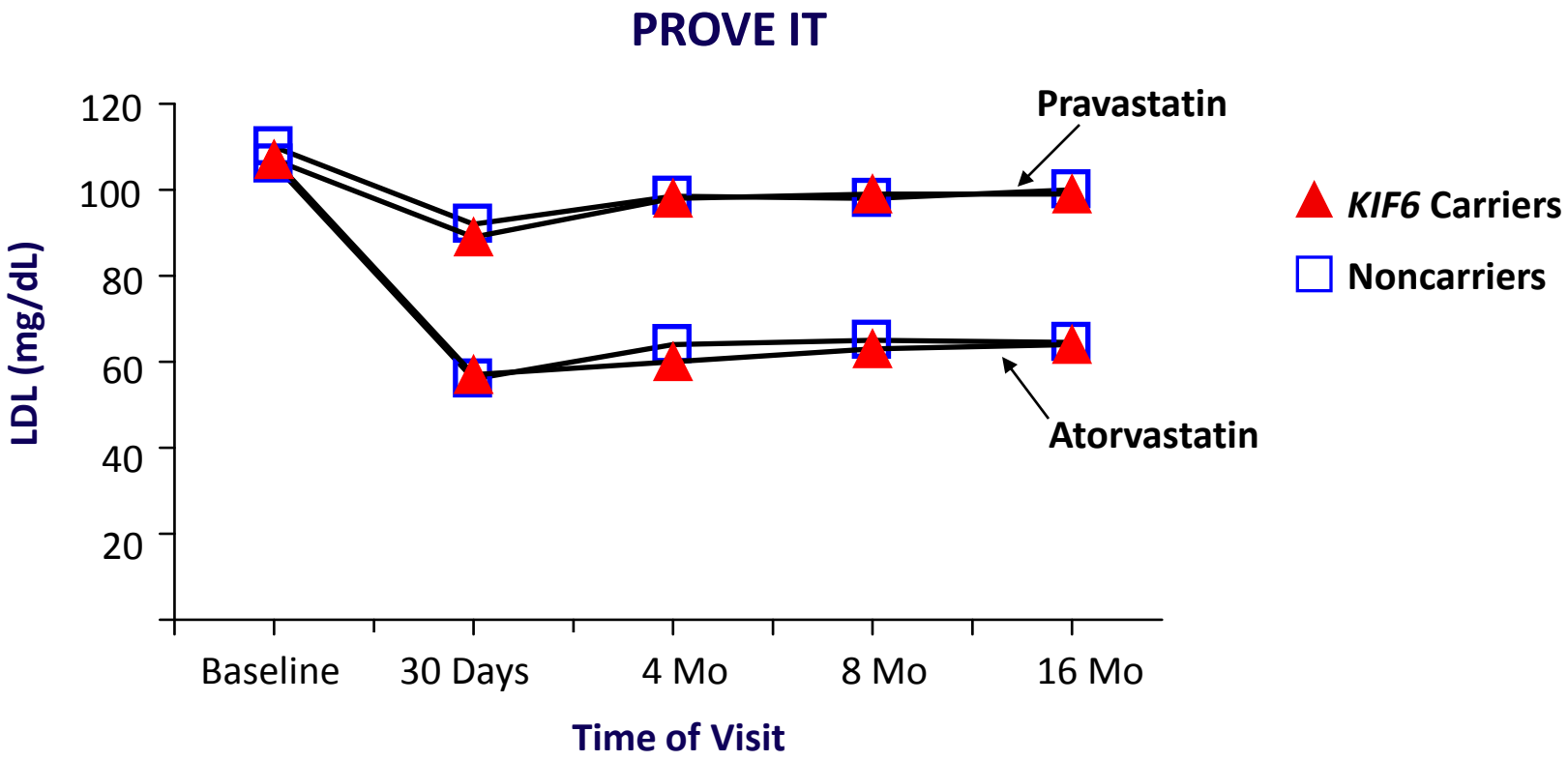
Results From the PROVE IT-TIMI 22 Study

Olga A. Iakoubova, MD, PhD,* Marc S. Sabatine, MD, MPH, FACC,† Charles M. Rowland, MS,* Carmen H. Tong, BS,* Joseph J. Catanese, BS,* Koustubh Ranade, PhD,‡ Katy L. Simonsen, PhD,‡ Todd G. Kirchgessner, PhD,‡ Christopher P. Cannon, MD, FACC,† James J. Devlin, PhD,* Eugene Braunwald, MD, MACC†

Alameda, California; Boston, Massachusetts; and Princeton, New Jersey

LDL-C Lowering by Statin Therapy

Similar Reduction in KIF6 Carriers and Noncarriers

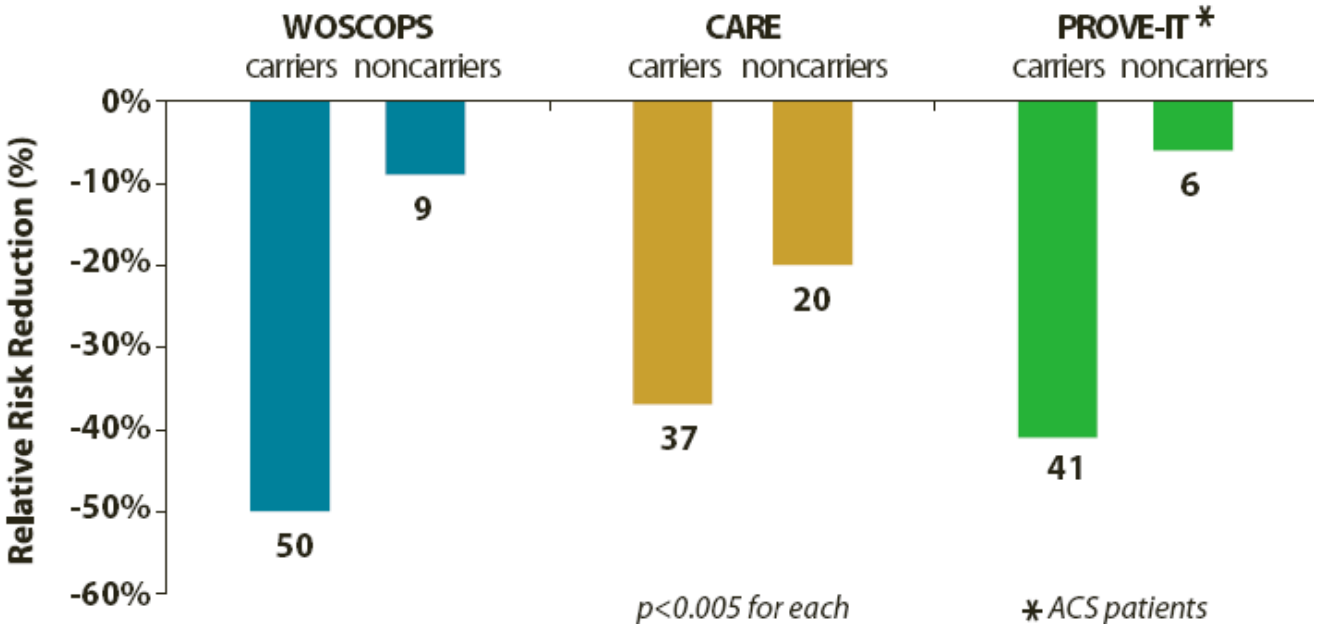


- Similar reduction of LDL-C levels in carriers and noncarriers
- However, event reduction was significantly greater in carriers

KIF6 719Arg Variant and CHD

Summary

- Associated with risk of CHD in 5 prospective studies
  - ARIC, WHS, CHS, CARE, and WOSCOPS
- 60% of Caucasians carry the risk allele, carriers are at up to 50% higher risk
- Risk estimate unchanged after adjustment for traditional risk factors
- Carriers received significant event reduction from statin therapy
  - Standard-dose pravastatin vs placebo
  - High-dose atorvastatin vs standard-dose pravastatin



CVD PREVENTION & PHARMACOGENETICS

MULTIPLE OTHER EVIDENCES....

1. Pharmacogenetics of CETP, PCSK9 (statins)…

2. AT and BK receptors polymorphisms (ACE-i, ARBs)…

3. Variable response to warfarin – CYP2C9 and VKORC1 variants…

4. Resistance to clopidogrel pharmacogenetics…

Health care (reforms?) into the future

- **Integrated health care**
  - **Primary**
  - **Secondary**
  - **Tertiary**

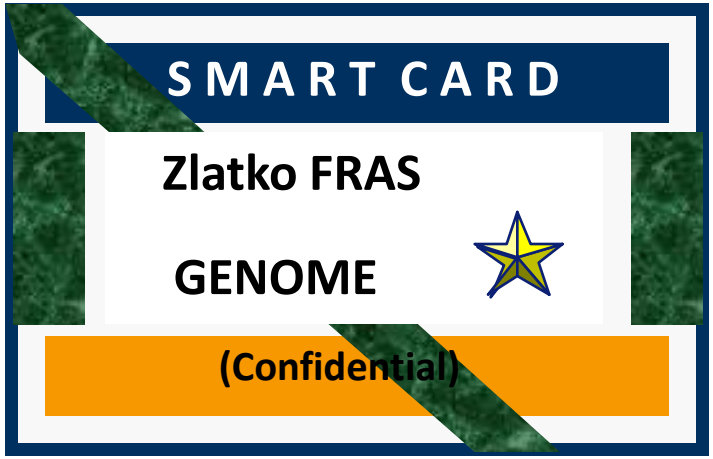
- **e-Health**
  - **Integrated data management**
  - **Electronic medical records**
  - **Population level planning and resource allocation**

- **Personalized Medicine** ⟷ **"back to the future" ?**

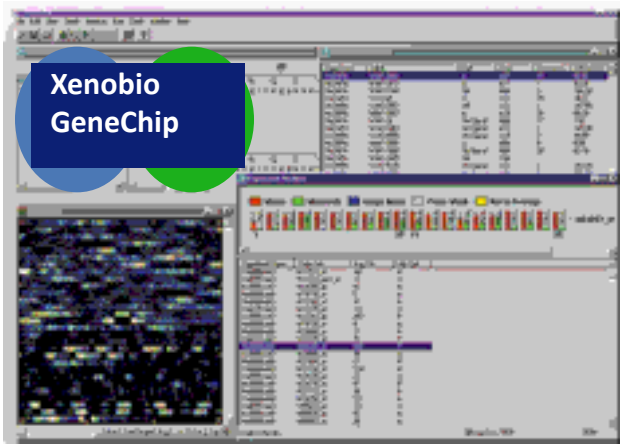
Personal genomics in medicine – The future

- **Cost of sequencing genomes dropping - $1000 genome**
  - Analysis and understanding will remain expensive
- **Every child born or patient will likely have his or her genome sequenced fully**
- **This genome record should allow physicians to make treatment decisions based on patients genotypes:**
  - **will allow individuals to make appropriate lifestyle choices (food, exercise... etc)**
  - **will allow to use appropriate drugs**
- **Genome data will allow rapid drug development**

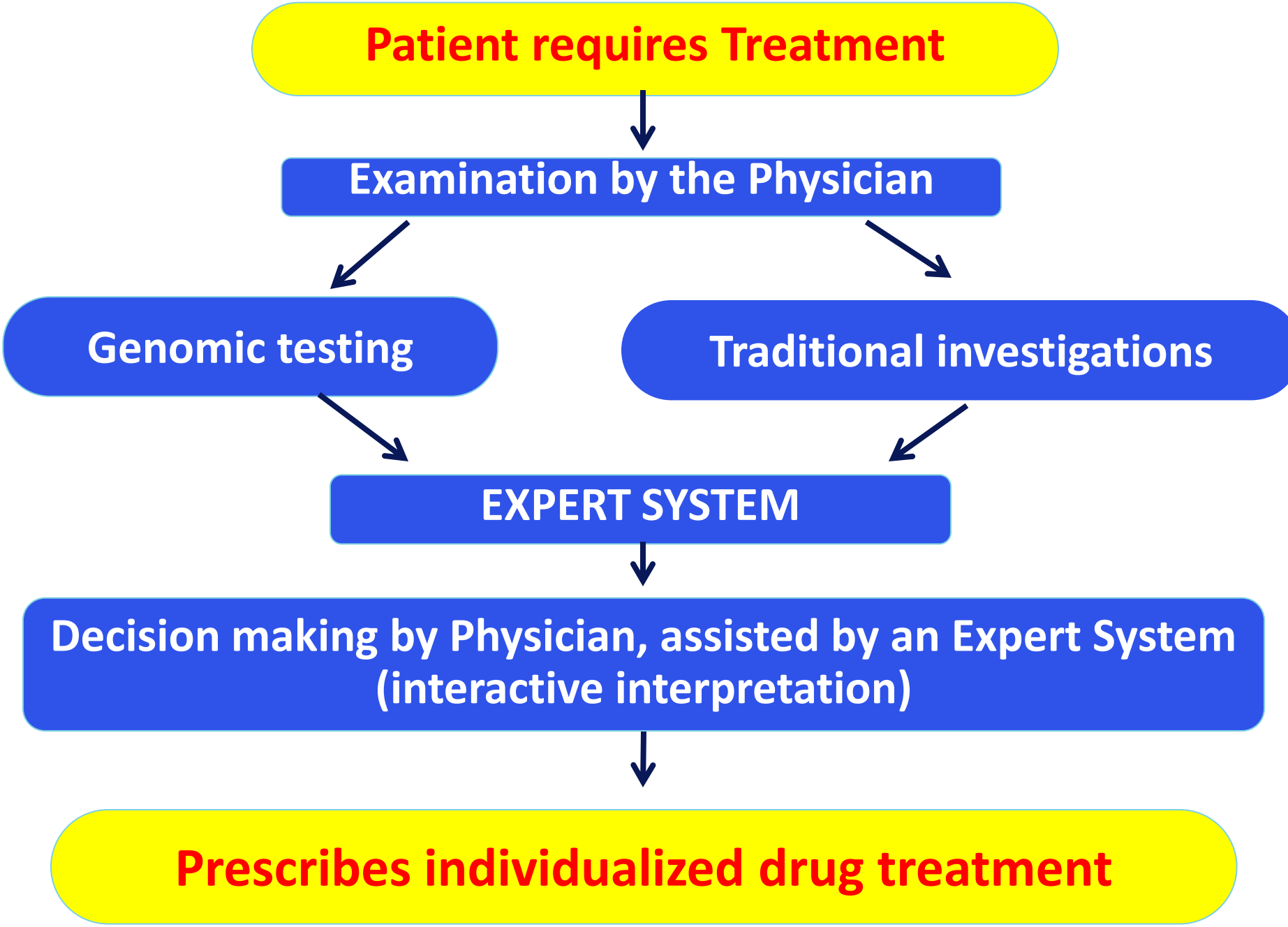
Personalized Medication in the Future



Gene Chip Analysis



In the future (? years), doctors will be able to select the best drug to treat your disease and the appropriate dose based on knowledge of your specific genetic makeup!


Patient requires Treatment
Examination by the Physician
Genomic testing
Traditional investigations
EXPERT SYSTEM
Decision making by Physician, assisted by an Expert System (interactive interpretation)
Prescribes individualized drug treatment

The Promise of Pharmacogenomics

1. "Pharmacogenomics will radically change the manner in which we develop drugs."

How close we really are?

3. "Applying pharmacogenomics to drug development will cut cycle times to 1.5 - 2 years."

4. "Pharmacogenomics will be able to bring removed drugs back on the market, by predicting who is susceptible to adverse events."

Conclusions

We look to a future in which medicine will be predictive, preventive, preemptive and

(again) personalized…

This will immediately lead to

(very) significant changes of some common and also very fashionable current concepts

(e.g. evidence-based medicine, guidelines with "one-size fits for all" recommendations, etc.)…

Two Ethically Important Distinctions

You know these, but it is important not to forget them…

Research/therapy and *subject/patient*

- **research is aimed at developing new knowledge that may or may not benefit individual human subjects (it may even harm them); benefits usually enjoyed, if at all, by future patients**
- **therapy is aimed at benefiting an individual patient**
- **research supporting the development of personalized medicine, in particular, tends to blur the distinction between subject and patient**

Disclaimer

Personalized medicine in the framework of narrower, "contemporary" sense
(using genetics studies and treatment guidance)

remains
a research concept –

it is not yet ready for clinical practice…

…but….is it really so ?